REMARKS

In the Office Action dated October 10,2007, claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are under examination to the extent that these claims read on elected sequences. Claims 2-4, 7-11, 14-22, 24-26, 29-37, 42, 44, 46, 48 and 50-52, as well as claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 to the extent that these claims do not read on the elected sequences, are withdrawn from further consideration. Claims 1, 27 and 28 are objected to because of certain alleged informalities. Claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are also rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enabling support. Claims 1, 27 and 28 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by McIntosh et al. (U.S. Patent No. 6,767,896 B1). Claims 1, 27 and 28 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Olivera et al. (U.S. 2003/0109670 A1). Claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly unpatentable over claims 1-7 of co-pending Application No. 10/537,704.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claim Amendments

Claims 1, 5, 6 and 28 have been amended to further delineate the possible conservative amino acid substitutions or modifications within loop 1, i.e., substitution of Tyr with MeY, and substitution of Leu with Hle or Nle. Support for this amendment is found in

original claims 22 and 23, and in the specification, e.g., page 11, lines 4-5, and Table 2. New claims 53-54 are added to depend from claims 1, 5, and 6 in alternative, and further delineate the possible conservative amino acid substitutions for Gly and Lys within loop 1. Support for these claims is also found in the specification, e.g., page 11, lines 4-5. Claims 55-58 are added to depend on claims 1, 5 and 6 in alternative, and further delineate suitable amino acids for Xaa5 and Xaa6. Support for these claims is found in claims 18-21, and in Table 2 in the specification, for example. It is also respectfully submitted that peptides having specific combinations of amino acid substitutions are also set forth in SEQ ID NOS: 42, 47, 48 and 61. Claim 59 is added to depend on claims 1, 5 and 6 in alternative, and further delineates the disulfide bonding pattern in the present connotoxin peptides, as disclosed on page 3, lines 17-24. No new matter is introduced by the foregoing amendments.

Restriction and Election

In the Action, the Examiner has made the Restriction Requirement final, and has examined claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 to the extent that these claims read on elected sequences. As indicated by the Examiner, the elected sequences are SEQ ID N O: 5 or SEQ ID NO: 3 in which Xaa1 is pyroglutamate, Xaa2 is absent, Xaa3 is G and Xaa4 is V, and Xaa5 and Xaa6 are both present and are any amino acid but Cys. Essentially, the elected sequences are EGVCCGYKLCXXC in which X is not C, and CCGYKLCXXC in which X is not C.

Applicants observe that the Examiner has correctly included claims 27-28 in the group of claims for examination, even though these claims were grouped with claims of (non-elected) Group I in the previous Action.

Applicants respectfully submit that claim 24, which depends from claim 1, should also be included in the examination. Claim 24 delineates the length of the claimed peptide to consist of "from 11 to 20 amino acids". In this connection, Applicants observe that claim 1 is drawn to a peptide comprising SEQ ID NO: 3, a 10-mer sequence; and SEQ ID NO: 5 is a 13-mer sequence. Therefore, Applicants respectfully request that the Examiner reconsider and examine claim 24 to the extent that this claim reads on a peptide comprising SEQ ID NO: 3 or SEQ ID NO: 5.

Claim Objection

Claims 1, 27 and 28 are objected to because of certain alleged informalities. Specifically, the Examiner objects to the recitation "neuronal amine/noradrenaline transporter" in claims 1, 27 and 28.

Applicants have amended claims 27 and 28 to recite "a neuronal amine transporter", to be consistent with the recitation in claim 1. Withdrawal of the objection is therefore respectfully requested.

35 U.S.C. §112, First Paragraph

Claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Further, Claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are also rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enabling support. Because both rejections are directed to conservative amino acid substitutions of G, Y, K and/or L in SEQ ID NOS: 3 and 5, Applicants will address the rejections together as follows.

The Examiner contends that the claims encompass an infinite genus of variants of SEQ ID NOS: 3 and 5 in which G, Y, K and/or L are replaced by any "conservative" amino acid substitution. According to the Examiner, the term "conservative amino acid substitution" is not defined in the specification, and only one or two examples are provided for each of these amino acids in isolation.

Further, the Examiner is of the opinion that the specification does not reasonably provide enablement for a polypeptide that is a variant of SE ID NOS: 3 or 5 having conservative amino acid substitutions for G, Y, K and/or L. The Examiner alleges that the specification contains no working examples disclosing any conservatively substituted variants of SE ID NOS: 3 or 5. Therefore, the Examiner concludes that undue experimentation is needed to establish that any conservatively substituted variant of SEQ ID NOS: 3 or 5 has the conotoxin activity of SEQ ID NOS: 3 or 5.

Applicants respectfully submit that the term "conservative substitution" is well understood by those skilled in the art. Further, contrary to the Examiner's allegation, this term is also defined in the specification. For example, the specification states on page 10, line 30 to page 11, line 3:

> "Substitutions encompass amino acid alterations in which an amino acid is replaced with a different naturally-occurring or a non-conventional amino acid residue. Such substitutions may be classified as "conservative", in which case an amino acid residue contained in a polypeptide is replaced with another naturally-occurring amino acid of similar character either in relation to polarity, side chain functionality or size, ..."

Further, the specification provides examples of conservative substitutions for Gly, Leu, Lys, and Tyr on page 11, lines 3-18:

"...for example Ser↔Thr↔Pro↔Hyp↔Gly↔Ala, Val↔Ile↔Leu, His↔Lys↔Arg, Asn↔Gln↔Asp↔Glu or Phe↔Trp↔Tyr. It is to be understood that some non-conventional amino acids may also be suitable replacements for the naturally occurring amino acids. For example Lys residues may be substituted by ornithine, homoarginine, *nor*-Lys, N-methyl-Lys, N,N-dimethyl-Lys and N,N,N-trimethyl-Lys. Lys residues can also be replaced with synthetic basic amino acids including, but no limited to, N-1 (2-pyrazolinyl)-Arg, 2-(4-piperinyl)-Gly, 2-(4-piperinyl)-Ala, 2-[3-(2S)pyrrolininyl]-Gly and 2-[3-(2S)pyrolininyl]-Ala. Tyr residues may be substituted with 4-methoxy tyrosine (MeY), *meta*-Tyr, *ortho*-Tyr, nor-Tyr, ^{125}I-Tyr, mono-halo-Tyr, di-halo-Tyr, O-sulpho-Tyr, O-phospho-Tyr, and nitro-Tyr. Tyr residues may also be substituted with a 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho derivatives. Tyr residues may also be substituted with the 3-hydroxyl or 2-hydroxyl isomers (meta-Tyr or ortho-Tyr, respectively) and corresponding O-sulpho- and O-phospho derivatives. Tyr residues can also be replaced with synthetic hydroxyl containing amino acids including, but not limited to 4-hydroxymethyl-Phe, 4-hydroxyphenyl-Gly, 2,6-demethyl-Tyr and 5-amino-Tyr. Aliphatic amino acids may be substituted by synthetic derivatives bearing non-natural aliphatic branched or linear side claims C_nH_{2n+2} up to an including n=8."

Moreover, the specification provides, in Table 2, examples of peptides containing specific conservative substitutions of Tyr with MeY, and Leu with Hle or Nle. Assay results using peptides containing these substitutions are provided in Table 4 in the specification. Combinations of these substitutions are also presented in SEQ ID NOS: 42, 47, 48 and 61. Therefore, ample guidance is provided in the specification with respect to variants of SEQ ID NOS: 3 and 5 in terms of conservative substitutions of G, Y, K and/or L.

In an effort to favorable advance prosecution, Applicants have amended claims 1, 5, 6, and 28 to further define the substitutions of Y and L, i.e., substitution of Tyr with MeY, and substitution of Leu with Hle or Nle, as supported by the specification. Additionally, Applicants have added claims 53-54 to delineate the suitable amino acid substitutions for Gly and Lys, as disclosed on page 10 of the specification.

In view of the foregoing amendments and remarks, it is respectfully submitted that the claims, as presently recited, fully satisfy the enablement and written description requirements under 35 U.S.C. §112, first paragraph. As such, withdrawal of the rejections is respectfully requested.

35 U.S.C. §102(e)

Claims 1, 27 and 28 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by McIntosh et al. (U.S. Patent No. 6,767,896 B1).

According to the Examiner, McIntosh et al. disclose polypeptides of SEQ ID NO: 12 and SEQ ID NO: 14, which comprise the conotoxin peptide Mar1. The Examiner indicates that SEQ ID NO: 12 and SEQ ID NO: 14 both "comprise" SEQ ID NO: 3 (CCGYKLCXXC) of the present application.

Applicants respectfully submit that SEQ ID NO: 12 and SEQ ID NO: 14 are both polypeptides of 61 amino acids, and represent a "propeptide" that, as admitted by McIntosh et al. (col. 20, lines 49-51), requires post-translationally processing in order to give rise to the smaller mature neuroactive toxins (i.e., conotoxin peptides). Unlike the presently claimed "χ-conotoxin peptide having the ability to inhibit neuronal amine transporter", there is no evidence provided in McIntosh et al. or elsewhere demonstrating that these 61 amino acid propeptides are "χ-conotoxin" peptides, or have an ability to inhibit neuronal amine transporter. In this connection, Applicants respectfully direct the Examiner's attention to new claim 59, which delineates the disulfide bonding pattern characteristic of a "χ-conotoxin peptide", as disclosed on page 3, lines 17-24 of the specification.

Therefore, Applicants respectfully submit that McIntosh et al. do not teach the claimed invention. Withdrawal of the §102(e) rejection based on McIntosh et al. is respectfully requested.

Claims 1, 27 and 28 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Olivera et al. (U.S. 2003/0109670 A1).

According to the Examiner, Olivera et al. disclose a polypeptide of SEQ ID NO: 351, which comprises the conotoxin polypeptide Mr1.1. The Examiner alleges that SEQ ID NO: 351 comprises SEQ ID NO: 3 (CCGYKLCXXC) of the present application.

It is observed that SEQ ID NO: 351 disclosed by Olivera et al. sets forth a nucleotide sequence. SEQ ID NO: 352, on the other hand, sets forth a polypeptide sequence that includes the CCGYKLCXXC peptide.

Similar to McIntosh et al., the polypeptide of SEQ ID NO: 352, disclosed by Olivera et al., consists of 62 amino acids and also represents a "propeptide" that is believed to require post-translationally processing in order to give rise to a smaller mature neuroactive toxin. Unlike the presently claimed "χ-conotoxin peptide having the ability to inhibit neuronal amine transporter", there is no evidence provided in Olivera et al. or elsewhere demonstrating that this 62 amino acid propeptide is a "χ-conotoxin peptide", or has an ability to inhibit neuronal amine transporter. Therefore, Applicants respectfully submit that Olivera et al. do not teach the claimed invention. Withdrawal of the §102(e) rejection based on Olivera et al. is respectfully requested.

Double Patenting

Claims 1, 5, 6, 12-13, 23, 27, 28, 38-41, 43, 45, 47 and 49 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly unpatentable over claims 1-7 of co-pending Application No. 10/537,704.

Applicants recognize that this is a provisional rejection because the conflicting claims have not in fact been patented. Applicants also recognize that the rejection can be overcome by a timely filed terminal disclaimer. Applicants will address this rejection once the claims are found otherwise allowable.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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